A Dissertation on

ELEVATED FIRST TRIMESTER SERUM URIC ACID AS A PREDICTOR FOR THE DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

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BONAFIDE CERTIFICATE

Certified that this dissertation is the bonafide work of Dr. PARVATHY.N on ***ELEVATED FIRST TRIMESTER SERUM URIC ACID AS A PREDICTOR FOR THE DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS*** during her M.D.,(Obstetrics & Gynaecology) course from April 2009 to April 2012 at the Stanley Medical College and Raja Sir Ramasamy Mudaliar Lying-in Hospital, Chennai.

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In keeping with the maxim, "All is well that ends well", I was able to carry out my study to my fullest satisfaction, thanks to guidance, encouragement, motivation and constant supervision extended to me, by my beloved Chief *Prof.* ***Dr.D.Tamilselvi,*** M.D., Professor and Chief of Unit V. Hence my profuse thanks are due for her.

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CONTENTS

INTRODUCTION

INTRODUCTION

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during present pregnancy. This definition applies whether or not insulin is used for treatment. Uric acid is associated with insulin resistance in non pregnant women. Outside of pregnancy, hyperuricemia is also associated with the markers of metabolic syndrome, including obesity and dyslipidemia.

Uric acid is an independent risk factor for developing type 2 diabetes mellitus within 10 years in non pregnant adults, an association that was stronger in women compared to men.

Uric acid is the end product of purine metabolism catalyzed by enzyme xanthine oxidase/ dehydrogenase. In pregnancy uric acid is correlated with insulin resistance in women with gestational hypertension and higher at 24- 28 weeks of gestation in women diagnosed with GDM compared to women without diabetes. Uric acid is also higher in non pregnant women with a history of gestational diabetes, independent of body mass index. Since uric acid is associated with insulin resistance and predates development of type 2 diabetes in non pregnant adults, we hypothesis that higher uric acid in the first trimester would be associated with development of gestational diabetes.Compared with pre-pregnancy values uric acid concentrations decreased significantly by 8 weeks gestation and this reduced level maintained until about 24 weeks.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during present pregnancy. This definition applies whether or not insulin is used for treatment.

A Short History of Gestational Diabetes as a Clinical Entity

Gestational Diabetes as a clinical entity officially began in 1979 when the National Diabetes Data Group (NDDG) issued an updated classification of diabetes types, including one that was present only during pregnancy. In 1979, the First International Workshop-Conference on Gestational Diabetes Mellitus also met, essentially declared Gestational Diabetes a disease, finding it a significant health risk that needed treatment. Instead of the more neutral "Carbohydrate Intolerance of Pregnancy", the term "Gestational Diabetes Mellitus" was used (often shortened in various resources to Gestational Diabetes, GD, or GDM). Authorities felt that if the term 'diabetes' was used, women would be more likely to take the diagnosis seriously and insurance companies would be much more likely to cover treatment for it.

However, the idea of sub clinical glucose levels in pregnancy affecting mother or baby (or being an early sign of future full-blown diabetes) had been discussed previously**.**

Hadden et al (1998) reports incidents in the medical literature appearing as early as 1823 where diabetic-like conditions presented during pregnancy but seemed to disappear afterwards. However, greater attention to the concept that lesser degrees of hyperglycemia might negatively affect a pregnancy began to appear in the 1940s and 1950s. In these studies, researchers found increased perinatal mortality among the babies of women who developed diabetes years later, leading to the coining of the term "prediabetes in pregnancy."

Belgian researcher J.P. Hoet et al published a study on "Carbohydrate Metabolism During Pregnancy" and first used the term, "metagestational diabetes" in 1954. His investigations sparked a series of investigations in the 50s and 60s.

Jorgen Pedersen et al probably was the first to use the modern term "gestational diabetes" in 1967, and this was the term promoted **by Dr. Norbert Freinkel** and associates, later adopted by the First International Workshop-Conference on Gestational Diabetes Mellitus.

The first major prospective study was established in Boston in 1954, and the 1-hour 50-gram glucose screening test was first used there.

The results from this Boston study were presented by **O'Sullivan and Mahan et al in 1964**, and showed that higher blood glucose values in pregnancy correlated with the development of diabetes later in life.

In October 1979**, Dr. Norbert Freinkel et al** (representing the American Diabetes Association) and **Dr. John Josimovich et al** (representing the American College of Obstetricians and Gynecologists) met in Chicago at the First International Workshop Conference on Gestational Diabetes Mellitus. They gathered together experts from around the world to share their clinical experience, research, and opinions about GDM. Between this conference and the re-classifications from the National Diabetes Data Group, Gestational Diabetes as an official clinical entity was born. It is now defined as, "**Carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy. The definition applies whether insulin is used for treatment or the condition persists after pregnancy but does not exclude the possibility that the glucose intolerance may have antedated the pregnancy."**

PREVALENCE OF GDM

Globally, the quoted prevalence of GDM ranges from 1 - 16% (Agarwal, Dhatt, Punnose & Koster, 2005). This may be in part due to the different screening and diagnostic strategies employed to identify the condition and the particular population studied. The Australian Carbohydrate Intolerance Study (ACHOIS) undertaken in 14 centers in Australia and 4 centres in the United Kingdom reported that GDM affected 2 - 9% of all pregnancies (Crowther et al, Hiller et al, Moss et al, McPhee et al, Jeffries & Robinson et al, 2005). Whilst, Tuffnell et al, West et al and Walkinshaw et al (2003) in their systematic review of treatments for GDM and impaired glucose tolerance (IGT), for the 7 Cochrane Database state that 3-6% of all pregnancies are affected by GDM and IGT.

Terminology in the literature, relating to disturbances of carbohydrate metabolism in pregnancy can be confusing. In 1985, the World Health Organization (WHO) classification subdivided abnormal glucose tolerance in pregnancy into three categories defined by fasting venous glucose levels and venous plasma glucose values two hours after a 75gram oral glucose load (Nordin et al, Wei et al, Naing et al and Symonds et al, 2006). The three classifications were impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and GDM. The revised WHO classification (1999) now defines GDM as any abnormal carbohydrate metabolism first recognized, or diagnosed in pregnancy, regardless of severity. Remnants of the earlier classification are still encountered in the literature.

PATHOGENESIS

Pregnancy is a condition of

1) Accelerated starvation
2) Facilitated anabolism
3) Hyperinsulinism
4) Insulin resistance.

1.Accelerated starvation

There is fasting hypoglycemia because

- Glucose is diverted to fetus by facilitated diffusion.
- Increase insulin secretion during pregnancy.
- Amino acid acids diverted to fetus by active transport leading to substrate deficiency syndrome in the mother.
- Mother uses fat as a fuel resulting in ketogenesis

2. Facilitated Anabolism

Prolonged hyperglycemia after eating because of

- Increase absorption from gut
- Delayed glucose exchange from blood.
- Decrease uptake by muscles and splanchnic tissues.
- Decrease conversion to glycogen in liver.

3. Hyperinsulinism

Increase in estrogen and progesterone leads to

- β cell hyperplasia there by leading to increase insulin secretion.
- Increase sensitivity of β cells to glucose load.
- Increase suppression of glucose after meals.

4. Insulin Resistance

- Hormones

  HPL and prolactin

- Android obesity

  Increase omental and mesenteric fat.

- αTNF

  Impaired insulin signaling

  Inhibits insulin receptors tyrosine kinase activity.

  At the molecular level,there is decrease GLUT 4 protein transporter.

NDDG CLASSIFICATION

	New name	Old name
Type I	IDDM	Juvenile Diabetes
Type II	NIDDM	Adult onset
Type III		Gestational Diabetes

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Class	Onset	Fasting glucose	2 hours post prandial glucose	Therapy
A1	Gestational	<105mg/dl	<120mg/dl	Diet
A2	Gestational	>105mg/dl	>120mg/dl	Insulin
Class B – H similar to White's classification				

WHITE'S CLASSIFICATION OF DIABETES DURING PREGNANCY

Gestational diabetes	Discovered during pregnancy, glycemia may or may not be maintained by diet alone and insulin may be required
Class A	Discovered before pregnancy ,controlled with diet alone ,any duration or age of onset
Class B	Onset age 20 years or older, duration less than 10 years
Class C	Onset age 10 -19 years, duration 10 - 19 years.
Class D	Onset age under 10 years duration over 20 years, background retinopathy.
Class R	Proliferative retinopathy or vitreous hemorrhage.
Class F	Nephropathy with proteinuria over 500mg/day
Class RF	Criteria for both class R and F coexist
Class H	Atherosclerotic heart disease clinically evident
Class T	Prior renal transplantation

Risk assessment and timing of screening for Gestational Diabetes:

LOW RISK-

All of the following:

- Members of an ethnic group with a low prevalence of GDM.
- No known diabetes in first degree relatives.
- Age <25 years
- Weight normal before pregnancy
- Weight normal at birth.
- No history of abnormal glucose metabolism.

These patients blood glucose screening not routinely required.

AVERAGE RISK

One or more of the following:

- Member of an ethnic group with a high prevalence of GDM.
- Diabetes in a first degree relative.
- Age ≥25 years.
- Over weight before pregnancy.
- Weight high at birth.

These patients require blood glucose testing at 24-28 weeks (one or two Procedure).

HIGH RISK

- Marked obesity
- Strong family history of Type II DM.
- Previous history of GDM, impaired glucose metabolism or glucosuria.

These patients should perform glucose testing as soon as feasible.

HIGH RISK GESTATIONAL DIABETES
History of neonatal death
History of fetal macrosomia
Concomitant obesity and/or hypertension.
Development of oligohydramnios ,polyhydramnios,preeclampsia,or fetal macrosomia
Inadequate metabolic control with diet alone.

SCREENING TESTS

Surest screening procedure is estimation of blood glucose. **O'Sullivan and Mahan glucose challenge test** is the preferred test. Plasma glucose is measured 1 hour after 50 grams of oral glucose load without regard to the time of last meal. Plasma glucose >140 mg% - go for 3 hour 100 gram oral GTT.

Seshiah's spot test

Plasma glucose estimation is done in relation to the last meal.

Critical values -

0 hour -85 mg%

½ hour -95 mg%

1 hour -105 mg%

2 hour -105 mg%

2 hour 30 mts-95 mg%

3 hour -90 mg%

SOURCE OF SPECIMEN

- Plasma glucose is 14% higher than whole blood glucose level.
- Capillary blood glucose level is 20 mg% higher than whole blood level.
- Urine sugar on freshly voided urine alone with blood sugar gives some idea on renal threshold.

OTHER SCREENING TESTS

1) Glycosuria –glycosuria on the second fasting urine is significant. Also glycosuria if associated with ketonuria is significant. Normally 100 mg of glucose is excreted per day.If exceeded, can be measured by

Benedict's test.

Clinstix test.

Benedict's test is positive with all reducing sugars and with some drugs, so it is non specific.

Clinistix test is specific for glucose.

PIT FALLS-

- Blood sugar does not correlate with urine sugar always.
- Differs from person to person and on various occasions.
- Glycosuria is present in

  Diabetes mellitus

  Alimentary glycosuria

  Renal glycosuria

  Lactosuria

2) Instant blood glucose methods using strips and meters

Easy to perform

Venepunture not needed.

Quick results.

But lack precision

3) Glycosylated Hb (HbA1C)- Reflects glycemic control over last 2-3 months.

Normal range --- 5- 8%.

<8.5 % ---- good control.

8.5- 9.5%----fair control.

>9.5% ----poor control.

Variable values in renal failure.

Reduced in anaemia ,haemoglobinopathies and blood transfusion.

Costly test.

HbA1C in Ist Trimester

HbA1C in Ist trimester	Congenital anomalies	Abortions
<9.3 %	3%	12.4%
≥14.4%	4%	37.5%

4) Serum fructosamine assay.

Reflects glycemic control over last 2 weeks.

Normal value upto 285 µmol/L.

Reliable in anaemia & others.

Costly test.

GOLD STANDARD TEST

Gold standard test is the 3 hours 100grams oral glucose tolerance test.

Preparation of the patient.

- Unrestricted diet in the previous 3 days.
- Over night fasting of 8 -10 hours.
- Testing in the morning.
- Should be ambulant.
- Smoking should be avoided.
- Stop drugs – Phenytoin , Thiazides, OC pills, Steriods.
- Postpone after 3 weeks if major surgery/ stress.

PROCEDURE

After overnight fasting, fasting blood sugar is collected along with urine sugar.100grams of glucose is given. It can be dissolved in 200 ml of plain water or lime water to improve palatability. Venous blood is drawn for 3 hours along with urine**.**

DIAGNOSTIC CRITERIA

	O'Sullivan &Mahan (whole blood) mg/dl.	NDDG (Plasma)mg/dl	Carpenter &Coustan (Plasma) mg/dl	Sacks (Plasma)
Fasting	90	105	95	96
1Hour	165	190	180	172
2Hour	145	165	155	152
3 Hour	125	145	145	131

SPECIAL TESTS

Intravenous Glucose tolerance test (GTT)

25 grams glucose in 50%solution is given IV over 3 minutes. Blood sample is collected every 10 minutes for 1 hour.

Graph of blood glucose against time plotted.

K (Constant)=0.693 x 100/t½.

t½ - Time taken for blood glucose to fall to 50%of the value at 10 minutes.

Normal –K=1.2 TO 2.3.<1.2- Diagnosed as GDM.

Advantages

Short duration

Useful in patients with Malabsorption syndromes**.**

Disadvantages

Frequent collection

Non physiological so only for research purposes

INVESTIGATIONS

FOR CONFIRMATION – GTT

ROUTINE ANTENATAL INVESTIGATIONS

1. Urine for protein, sugar, and microscopic examination.
2. Hb
3. VDRL,HIV,HBsAg
4. Blood for grouping and Rh typing**.**

INVESTIGATIONS FOR ASSESSING GLYCEMIC STATUS.

INVESTIGATIONS FOR ASSESSING COMPLICATIONS

INVESTIGATION FOR ASSESSING GLYCEMIC STATUS:

- Urine sugar monitoring – unreliable.
- Blood sugar estimation is best.

In controlled GDM, DM, once in 2-4 weeks.

Self monitoring of blood glucose (SMBG) is mandatory in

- All the pregnant women on insulin.
- Patients with fluctuating glucose levels.
- Patients showing recurrent ketosis or hypoglycemia.
- In the perioperative period.

INVESTIGATIONS FOR ASSESSING COMPLICATIONS:

Infections

- Asymptomatic bacteriuria to be looked for at booking, 28, 32, 36 weeks.
- Vulval moniliasis screening
- Urine should be examined for proteins and microscopic deposits during each visit**.**

Diabetic nephropathy

- Urine for proteins using dipstick during each visits.
- If dipstick +ve 24 hours urinary protein for microalbuminuria.
- Renal function tests- blood urea, serum creatinine, serum electrolytes**.**

Diabetic retinopathy

- Measuring visual acuity
- Opthalmoscopic examination through dilated pupils

Stages

1. Non proliferative retinopaty.
2. Preproliferative retinopathy.
3. Proliferative retinopathy.

- Cononary heart disease and cardiomyopathy. ECG in all the leads and echocardiogram.
- Fasting lipid profile.
- Urine for ketone bodies and serum electrolytes in the presence of high blood sugar, persistent vomiting and infection

Screening for fetal anomalies:

- Glycosylated Hb estimation.
- Chorionic villous sampling.
- Maternal serum α fetoprotein estimation.
- Amniocentesis.
- Targeted ultrasound.
- Fetal echocardiogram

Ultrasound

Assessment of altered growth

Ultrasound every 4weeks from 20 weeks.

MACROSOMIA can be identified by

- AC and thigh diameter >90^{th} percentile.
- Head and femur measurements < 90^{th} percentile.
- Abdominal girth >head circumference.
- AC change >1-2 cm/week.
- Increase subcutaneous fat.

For assessing amniotic fluid volume.

For assessing placental position.

URIC ACID

Uric acid is the end product of purine metabolism. Purines are obtained from both dietary sources and from the breakdown of body proteins. Organ meats such as liver, kidneys, and sweetbreads, sardines, anchovies, lentils, mushrooms, spinach, and asparagus are all rich sources of purines. The kidneys excrete uric acid as a waste product. The kidneys excrete two-thirds of the uric acid produced daily; the remaining one-third is excreted in the stool.

The exact level of uric acid that is considered pathological is controversial. In recent years, it has been recognized that the normal ranges of uric acid are quite wide. Because of this wide range, and because uric acid levels show day-to-day and seasonal variations in the same person, several uric acids levels may be ordered over a period of time. Urine uric acid levels may also be used to evaluate gout or determine oversecretion of uric acid.

Reference values: Serum Uric Acid

- Adult males: 2.0 - 7.5 mg/dl
- Adult females**: 2.0 - 6.5 mg/dl; in early pregnancy uric acid levels fall by about one-third but rise to non-pregnant levels by term**
- Children (ages 10-18)
    - Males: 3.6 - 5.5 mg/dl; significant rise in males at ages 12-14 coincides with puberty.
    - Females: 3.6 - 4 mg/dl
- Elderly:
    - Males older than 40: 2 - 8.5 mg/dl

Females older than 40: 2 - 8.0 mg/dl; rise in women related to menopause

The normal range for **urinary uric acid** is between 250 - 750 mg over a 24-hour period. Uric acid levels tend to vary day to day. It is also important to check the laboratory reference values for each work setting.

An **elevated blood uric acid** level, also known as hyperuricemia, is seen in:

- Gout
- Renal disease and renal failure
- Alcoholism
- Dehydration
- Leukemia and lymphoma
- Starvation
- Metabolic acidosis
- Toxemia of pregnancy
- Infectious mononucleosis
- Hyperlipidemia
- Hemolytic anemia
- Excessive cell destruction associated with chemotherapy and radiation treatment

An overproduction of uric acid occurs when there is excessive cell breakdown and catabolism of nucleonic acids such as seen in gout, excessive production and destruction of cells, as may occur in leukemia or during cancer therapy, or problems with uric acid excretion due to renal failure.

Changes in serum uric acid concentrations during normal pregnancy:

Serial changes in serum uric acid concentrations have been studied in a group of healthy women before conception, at regular intervals throughout pregnancy and finally 12 weeks after delivery. Compared with pre-pregnancy values uric acid concentrations decreased significantly by 8 weeks gestation and this reduced level was maintained until about 24 weeks. Thereafter the concentrations increased such that by term they were greater than the pre-pregnancy values in the majority of patients and remained elevated until at least 12 weeks after delivery. If clinical management during the second half of pregnancy is to be based on increases in serum uric acid concentrations then such increases will have to be carefully interpreted against the background of rising concentrations which occur as part of the physiological response to normal pregnancy.

CHANGES IN NORMAL PREGNANCY

	Normal values of serum uric acid (mg/dl)
Non pregnant adult	2.5 – 5.6
First trimester	2.0 – 4.2
Second trimester	2.4 – 4.9
Third trimester	3.1 – 6.3

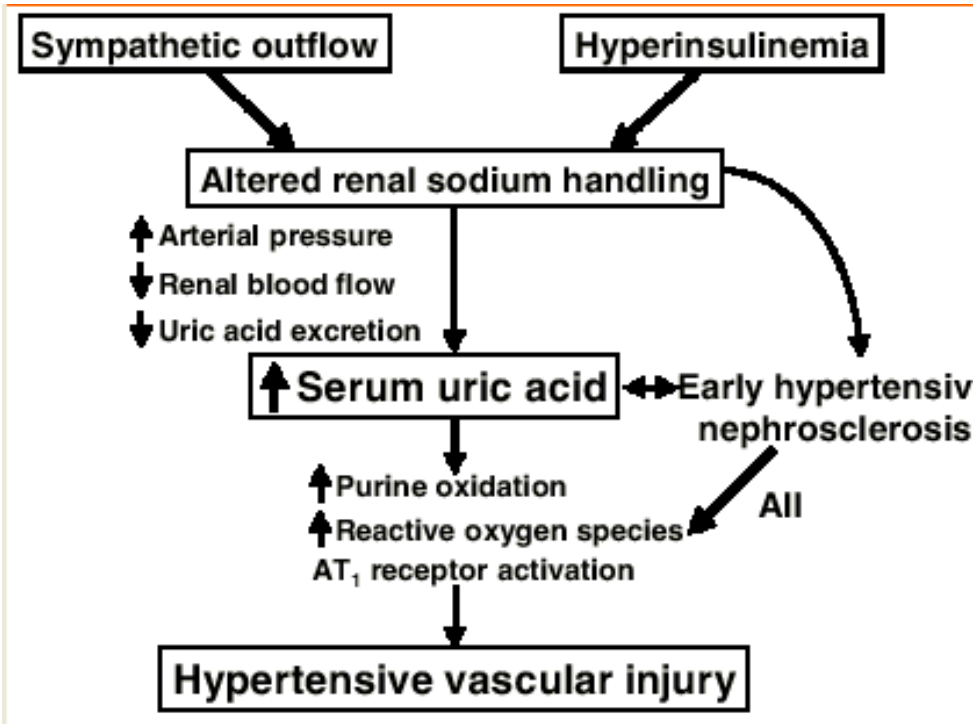
ASSOCIATION OF SERUM URIC ACID AND GDM:

It is possible that the association of uric acid with insulin resistance is causal. **Two mechanisms** have been hypothesized by which uric acid can cause insulin resistance. Nakagawa et al. proposed that uric acid causes endothelial dysfunction and decreases nitric oxide production by the endothelial cell. In animals, insulin's action on glucose uptake into cells in the skeletal muscle and adipose tissue is dependent on nitric oxide. Thus decrease in nitric oxide lead to decreased glucose uptake and the development of insulin resistance.

Another mechanism by which uric acid may induce insulin resistance may be that uric acid causes inflammation and oxidative stress in adipocytes, which is a contributor to the development of metabolic syndrome in mice.

First trimester hyperuricemia was associated with an increased risk of developing gestational diabetes mellitus. The risk of developing gestational diabetes was 3.25 fold higher if first trimester uric acid was in 4 th quartile. Although uric acid was strongly associated with body mass index, the risk of gestational diabetes was increased among women with elevated first trimester uric acid independent of BMI. Uric acid increases with increased protein intake, alcohol consumption, decreased excretion, or increased endogenous production.

Uric acid in the first trimester likely approximates pre-conception uric acid, and elevated uric acid may identify women who are predisposed to metabolic syndrome with an increased risk of developing GDM, independent of obesity. Alternatively, uric acid decreases early in pregnancy, so perhaps women with elevated uric acid have a poor adaptation to pregnancy (i.e. abnormal placentation), putting them at risk for adverse pregnancy outcomes such as GDM.



Many studies on the association between uric and GDM have been performed.

Zekai Tahir Burak et al studied Relationship between serum uric acid, creatinine, albumin and gestational diabetes mellitus at The Women's Health and Research Hospital, Ankara, Turkey, and found

Creatinine levels were significantly higher in the diabetic group than in the control group [0.6+/-0.15 vs. 0.43+/-0.1 mg/dL (53.04+/-13.26 micromol/L vs. 38.01+/-8.84 micromol/L), p<0.001]. Uric acid levels were also higher in the diabetic patients, this elevation was statistically significant [4.42+/-1.09 vs. 3.1+/-0.84 mg/dL (260.78+/-64.31 micromol/L vs. 231.49+/-49.56 micromol/L), p<0.001]. There were no differences in mean albumin concentrations or liver function tests.

Title: Hypertension in pregnancy: official journal of the International Society for the Study of Hypertension in Pregnancy Volume: - ISSN: 1525-6065 ISO Abbreviation:-Publication Date: 2010 Sep studied that High Uric Acid Level during the First 20 Weeks of Pregnancy is Associated with Higher Risk for Gestational Diabetes Mellitus and Mild Preeclampsia.

Results: Significant linear association was documented between UA level in the first 20 weeks and the prevalence of GDM and mild preeclampsia. The lowest and the highest prevalence of GDM were found in the UA </= 2.4 mEq/L group (6.3%) and in the UA > 5.5 mEq/L group (10.5%) (p < 0.001), respectively.

Samer Samir Lamey et al , in Heliopolis Hospital under supervision by Prof. Dr.Ali Farid Mohamed Ali Professor of Obstetrics & Gynecology Faculty of Medicine Ain Shams University,2010 studied the Risk of elevated body mass index in expectation the presence of gestational diabetes mellitus and associated elevated uric acid concentrations

Lind T, Godfrey KA, et al studied the Changes in serum uric acid concentrations during normal pregnancy. He found that compared with pre-pregnancy values uric acid concentrations decreased significantly by 8 weeks gestation and this reduced level was maintained until about 24 weeks. Thereafter the concentrations increased such that by term they were greater than the pre-pregnancy values in the majority of patients and remained elevated until at least 12 weeks after delivery.

Simmi Kharb et al studied the relation between Ascorbic acid and uric acid levels in gestational diabetes mellitus and found that Significantly low vitamin C levels were observed in GDM as compared to those in controls ($P<0.05$). Significantly high serum uric acid levels were observed in GDM as compared to those in controls ($P<0.05$).Vitamin C and uric acid levels showed a significant negative correlation ($r = 0.25$, $P<0.05$).

	Control group	Study group
Vit C	1.077±0.392	0.801±0.119
Uric acid	3.73±0.14	5.23±0.33

AIM OF THE STUDY

AIM OF THE STUDY

The aim of the study is to test the hypothesis that elevated uric acid measured in the first trimester of pregnancy are associated with the subsequent development of gestational diabetes mellitus.

MATERIALS AND METHODS

MATERIALS AND METHODS

This is a prospective study conducted in Government RSRM-lying in hospital attached to Stanley Medical College Chennai during October 2010 – November 2011.A total of 154 antenatal women belonging to first trimester were included in the study. The aim of the study was explained to the antenatal women and informed consent obtained.

INCLUSION CRITERIA -

Antenatal women with gestational age < 15 weeks.

EXCLUSION CRITERIA –

Pregestational diabetes mellitus

Renal disease

Liver disease

Cardiovascular disease

Gout

Smoking

Detailed history obtained from the patients. General examination was done. Per abdomen examination was done. Ultrasound was done to calculate the gestational age.

MEASUREMENT OF PLASMA URIC ACID:

Venous blood sample was withdrawn from antenatal women with gestational age <15 weeks. The samples were centrifuged to separate the

serum and stored at -70ºC till examined. Uric acid measured using colorimetric assay with detection limit of 10 mg/dl. The coefficient was 0.9%.

SCREENING FOR GDM

All antenatal mothers were followed up around 24-28 weeks for routine GDM screening with 50 grams of oral glucose challenge test (GCT).Those antenatal mothers with plasma glucose level after 1 hour ≥140 mg/dl, these women are considered high risk and are subjected to oral glucose tolerance test (OGTT).

ORAL GLUCOSE TOLERANCE TEST

After about 8 hours of fasting, those antenatal women with positive GCT (≥140mg/dl) are subjected to GTT. Fasting blood glucose is taken. After which 100 grams of glucose is taken oral. 1hr, 2hr, 3hr glucose levels are measured. Patients are considered to have GDM if two or more of the 4 values exceed the following:

Fifth international workshop conference on gestational diabetes-

Fasting - 95 mg/dl

1hr - 180 mg/dl

2hr - 155 mg/dl

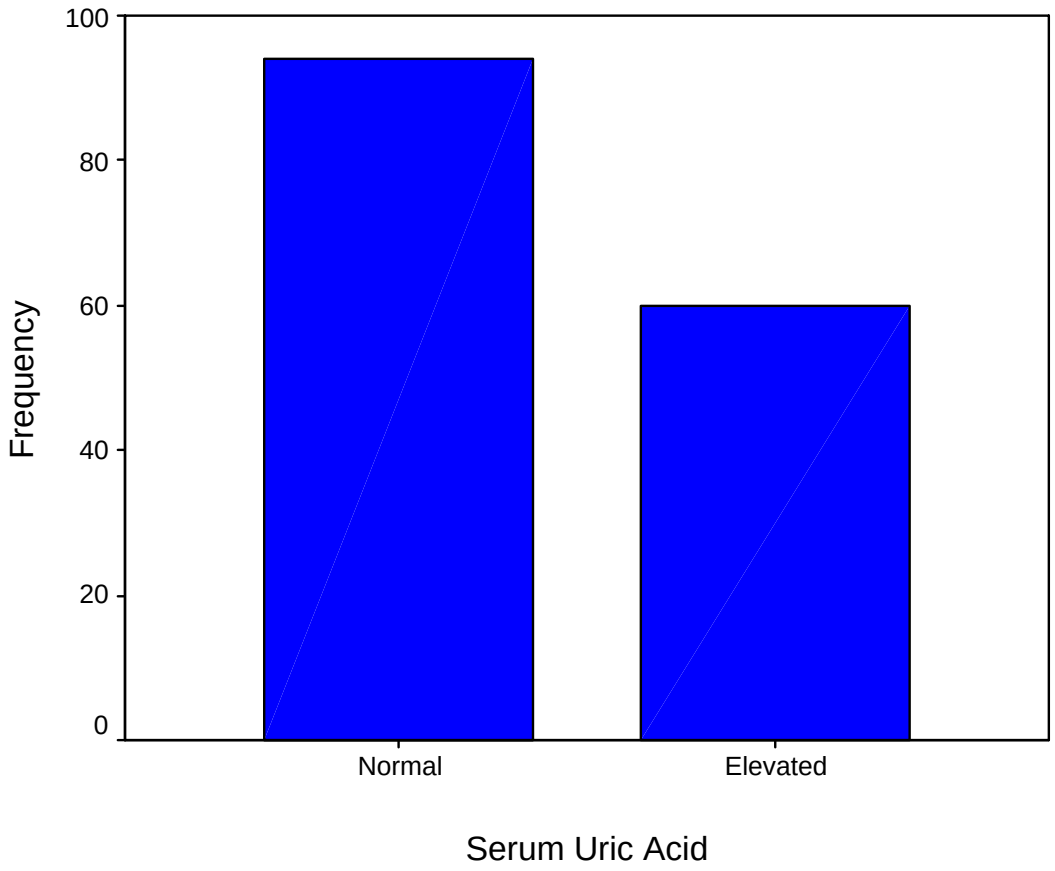
3hr - 140 mg/dl

Those antenatal women with positive GTT were admitted as in-patient and further evaluated. These antenatal women were managed with diet and some with both insulin and diet.

RESULTS

DISTRIBUTION OF SERUM URIC ACID

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	94	61.0	61.0	61.0
	Elevated	60	39.0	39.0	100.0
	Total	154	100.0	100.0	

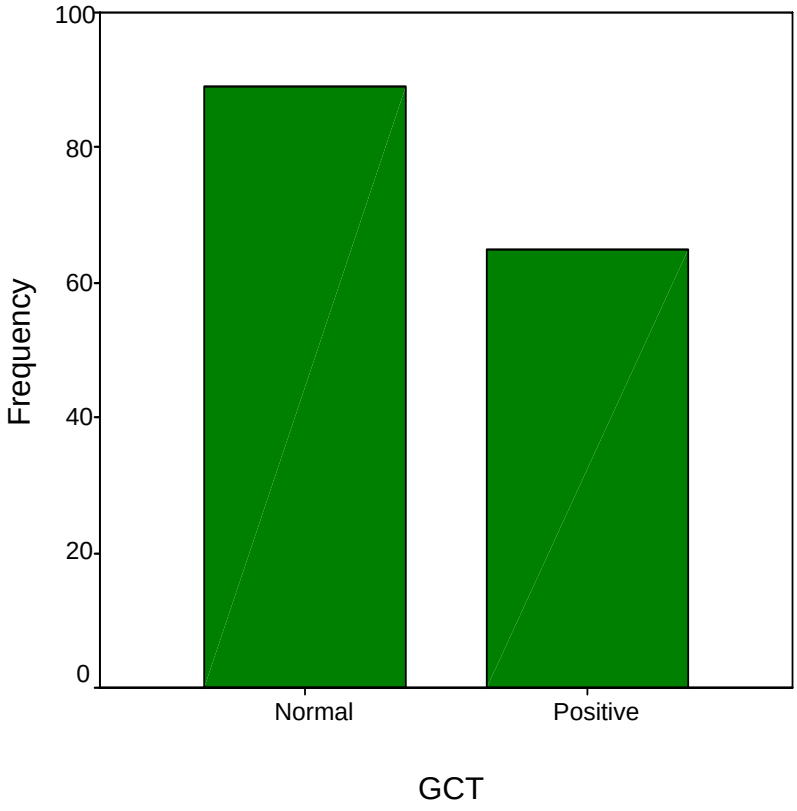


This table shows the distribution of serum uric acid among the total

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	89	57.8	57.8	57.8
	Positive	65	42.2	42.2	100.0
	Total	154	100.0	100.0	

antenatal patients. 94 patients had normal uric acid constituting about 61% and 60 patients had elevated uric acid constituting about 39%.

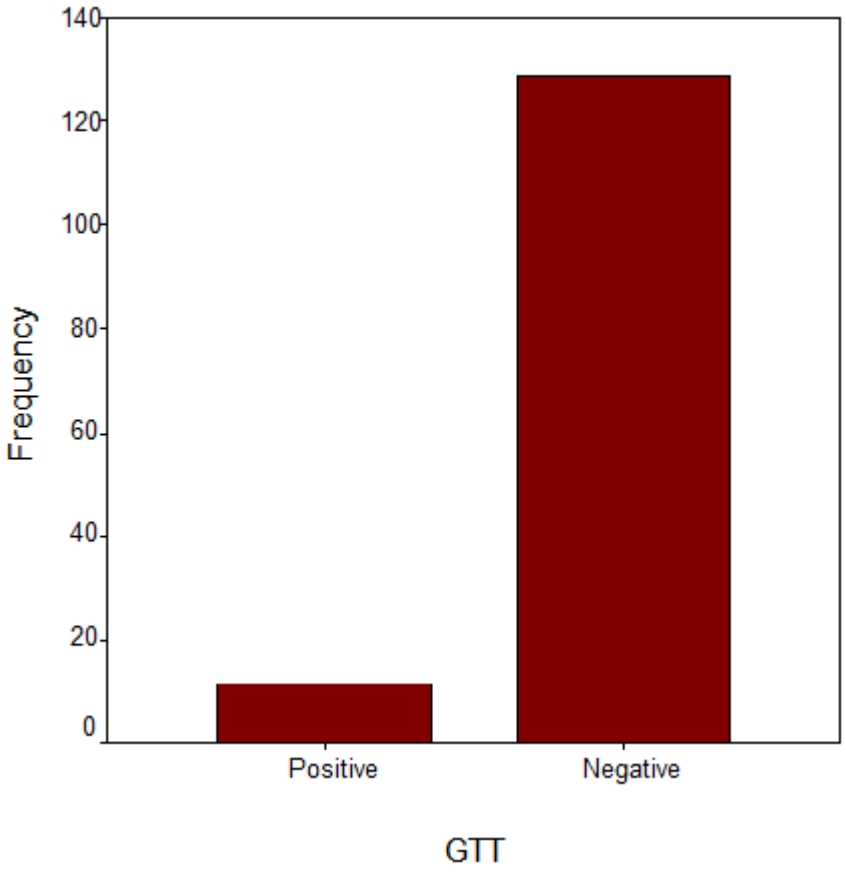
RELATIONSHIP BETWEEN SERUM URIC ACID AND GCT



This above table shows the relationship between serum uric acid and GCT. GCT was normal in 89 patients, constituting 57.8% and GCT was positive in 65patients constituting 42.2%

GLUCOSE TOLERANCE TEST

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Positive	13	6.4	6.4	6.4
	Negative	141	91.5	91.5	100.0
	Total	154	100.0	100.0	



This above table infers that 13 patients had GTT constituting 6.4% and 141 patients negative constituting 91.5%.

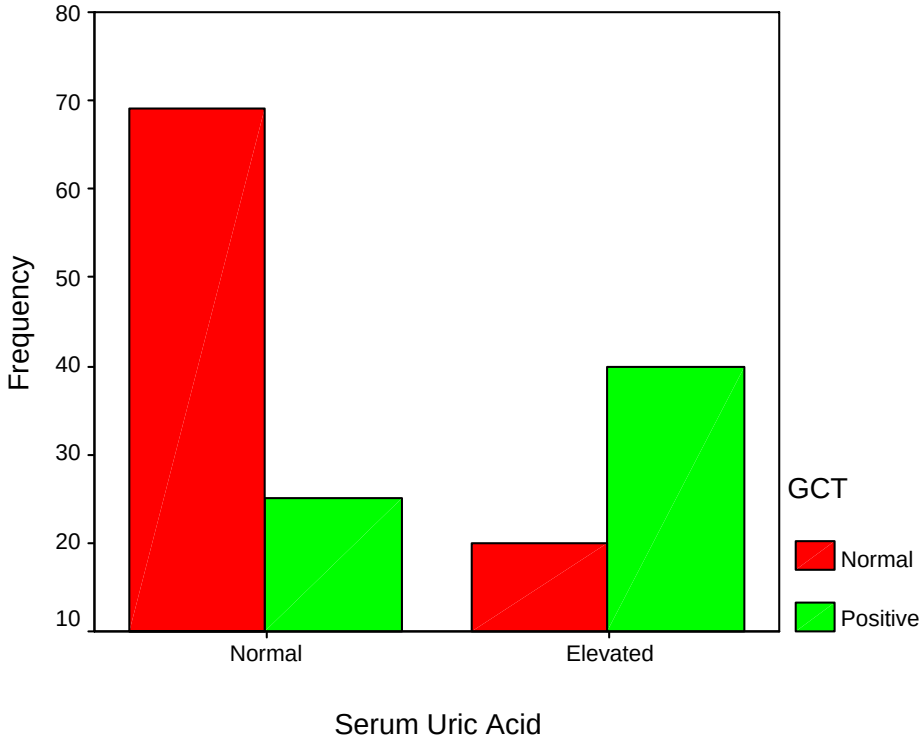
Serum Uric Acid * GCT Cross tabulation

			GCT		
			Normal	Positive	Total
Serum Uric Acid	Normal	Count	69	25	94
		% within Serum Uric Acid	73.4%	26.6%	100.0%
		% within GCT	77.5%	38.5%	61.0%
	Elevated	Count	20	40	60
		% within Serum Uric Acid	33.3%	66.7%	100.0%
		% within GCT	22.5%	61.5%	39.0%
Total		Count	89	65	154
		% within Serum Uric Acid	57.8%	42.2%	100.0%
		% within GCT	100.0%	100.0%	100.0%

In our study of the total patients (60) with elevated uric acid,20 patients had normal GCT – constituting 22.5%.And the remaining 40 patients with elevated uric acid had positive GCT constituting 61.5%.(>140 mg/dl).

And among those with normal uric acid total (94), 69 patients had normal GCT constituting 77.5% and 25 patients was positive for GCT with 38.5%.

RELATION BETWEEN SERUM URIC ACID AND GCT



Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	P value
Pearson Chi-Square	24.108(b)	1	.000			<0.001
Continuity Correction(a)	22.493	1	.000			
Likelihood Ratio	24.463	1	.000			
Fisher's Exact Test				.000	.000	
Linear-by-Linear Association	23.951	1	.000			
N of Valid Cases	154					

a Computed only for a 2x2 table

b 0 cells (.0%) have expected count less than 5. The minimum expected count is 25.32.

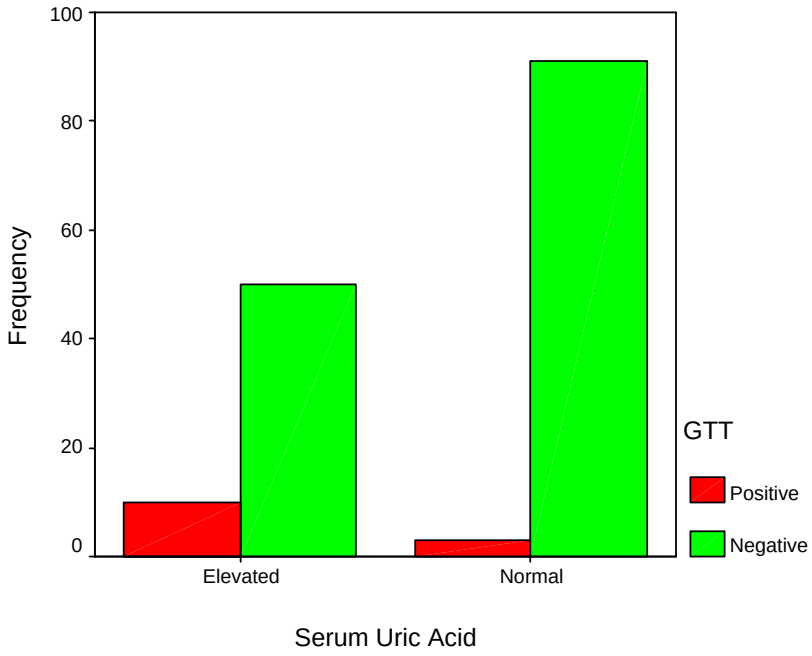
Serum Uric Acid * GTT Crosstabulation

			GTT		
			Positive	Negative	Total
Serum Uric Acid	Elevated	Count	10	50	60
		% within Serum Uric Acid	16.7%	83.3%	100.0%
		% within GTT	76.9%	35.5%	39.0%
	Normal	Count	3	91	94
		% within Serum Uric Acid	3.2%	96.8%	100.0%
		% within GTT	23.1%	64.5%	61.0%
Total		Count	13	141	154
		% within Serum Uric Acid	8.4%	91.6%	100.0%
		% within GTT	100.0%	100.0%	100.0%

In our study among the 60 patients with elevated uric acid ,10 patients were positive for GTT . And the remaining 40 were negative for GTT.

And among the 94 patients with normal uric acid only 3 were GTT positive.

RELATIONSHIP BETWEEN SERUM URIC ACID AND GTT



CHISQUARE TESTS

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.604(b)	1	.003		
Continuity Correction(a)	6.949	1	.008		
Likelihood Ratio	8.504	1	.004		
Fisher's Exact Test				.006	.004
Linear-by-Linear Association	8.548	1	.003		
N of Valid Cases	154				

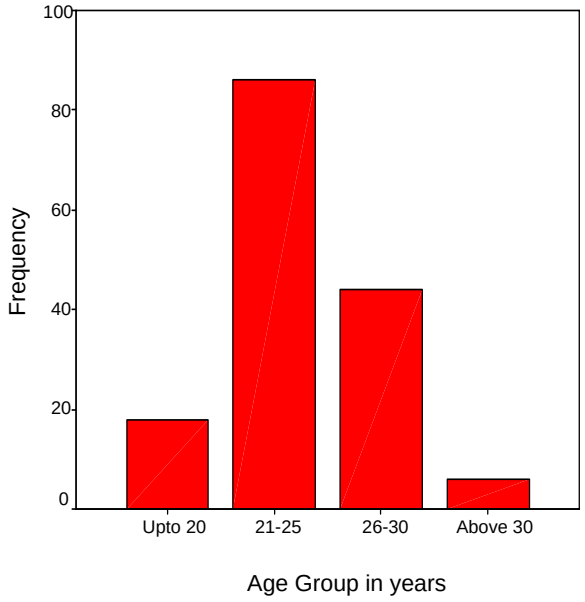
a Computed only for a 2x2 table

b 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.06.

In our study, maternal age had no much correlation with the serum uric acid. In our study age between 21 – 25 years had much frequency constituting 55.8%.

MATERNAL AGE (YEARS)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Upto 20	18	11.7	11.7	11.7
	21-25	86	55.8	55.8	67.5
	26-30	44	28.6	28.6	96.1
	Above 30	6	3.9	3.9	100.0
	Total	154	100.0	100.0	



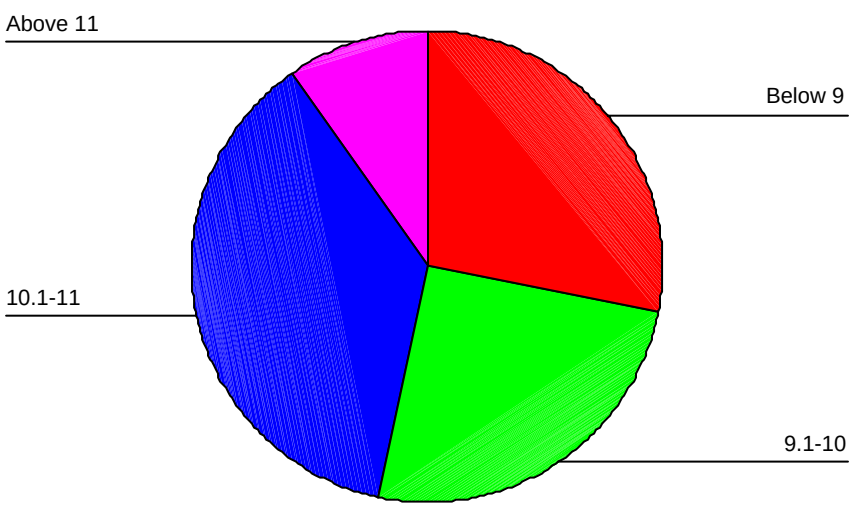
In a study by S. Katherine LAUGHON et al, The mean maternal age and gestational age at sampling decreased slightly with increasing uric acid quartile.

Gestational age in weeks

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Below 9	43	27.9	27.9	27.9
	9.1-10	39	25.3	25.3	53.2
	10.1-11	57	37.0	37.0	90.3
	Above 11	15	9.7	9.7	100.0
	Total	154	100.0	100.0	

In our study the frequency is high around 10.1 – 11 weeks.

And this had no much correlation within the first trimester.



Reliability of the test in predicting GDM

Sensitivity	specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio
76.9	64.5	2.678	0.383	6.991

Risk estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Serum Uric Acid (Elevated / Normal)	6.067	1.596	23.066
For cohort GTT = Positive	5.222	1.498	18.207
For cohort GTT = Negative	.861	.764	.970
N of Valid Cases	154		

In a similar study by S. Katherine LAUGHON et al, his hypothesis was the mean maternal age and gestational age at sampling decreased slightly with increasing uric acid quartile. Maternal pre-pregnancy BMI increased linearly with increasing uric acid quartile ($p<0.01$ for trend) and was associated with uric acid with an r^2 of 0.16 ($p<0.001$).

Of the 73 women who developed gestational diabetes mellitus, 34 (46.6%) had uric acid in the 4^{th} quartile and 39 (53.4%) had a BMI <30 kg/m^2.

Risk of gestational diabetes by first trimester uric acid quartile

	GDM n (%)	Adjusted OR* (95% CI)
1st (2.1)	7 (0.5)	ref
2nd (2.7)	12 (0.8)	1.62 (0.63-4.22)
3rd (3.2)	20 (1.3)	2.35 (0.96-5.78)
4th (4.2)	34 (2.2)	3.95 (1.35-7.83)

.

First trimester uric acid concentrations ≥3.6 mg/dl, (the highest quartile) were associated with a trend towards increased risk of developing gestational diabetes (adjusted OR=3.91; 95%CI: 0.75, 1.96) compared to women with concentrations below this concentration (lower three quartiles), after adjusting for BMI. Using a cut point of 3.6 mg/dl yielded a positive predictive value (PPV) of 12.0% and negative predictive value (NPV) of 96.7% for development of GDM. The area under the receiver operator curve was 0.7.

COMPARISION

	OUR STUDY	S. KATHERINE LAUGHON et al
Positive predictive value	**16.7**	**12**
Negative predictive value	**96.8**	**96.7**
Odds ratio	**5.2**	**3.9**

DISSCUSSION

DISSCUSSION

Pregnancy induces progressive changes in maternal carbohydrate metabolism. As pregnancy advances insulin resistance and diabetogenic stress due to placental hormones necessitate compensatory increase in insulin secretion. When this compensation is inadequate gestational diabetes develops

It is possible that the association of uric acid with insulin resistance is causal. Two mechanisms have been hypothesized by which uric acid can cause insulin resistance. Nakagawa et al. proposed that uric acid causes endothelial dysfunction and decreases nitric oxide production by the endothelial cell. In animals, insulin's action on glucose uptake into cells in the skeletal muscle and adipose tissue is dependent on nitric oxide. Thus, decreases in nitric oxide lead to decreased glucose uptake and the development of insulin resistance. Another mechanism by which uric acid may induce insulin resistance may be that uric acid causes inflammation and oxidative stress in adipocytes, which is a contributor to the development of metabolic syndrome in mice.

In our prospective study 154 antenatal women were included belonging to first trimester, who were attendees of Govt. RSRM Lying-in Hospital attached to Stanley medical college, during Dec 2010 to Nov2011. In our study of the total mothers who developed GDM 10 Antenatal mothers had elevated serum uric acid in first trimester, which constitute about 16.7(% within in GTT).And among 3 GDM mothers with normal serum uric acid constitute about 3(% within GTT).with p value <0.001)

In our study all antenatal women undertook glucose challenge test (GCT), more of a screening test. Of the normal uric acid GCT was positive among 25 mothers(constituting 26.6%).Of the elevated serum uric acid GCT was positive among 40 mothers(constituting 66.7%).With significant $p< 0.001$

The risk of developing gestational diabetes was 3.25-fold higher if first trimester uric acid was in the 4^{th} quartile. Although uric acid was strongly associated with body mass index, the risk of gestational diabetes was increased among women with elevated first trimester uric acid independent of BMI.

Our findings are consistent with the association of uric acid with insulin resistance in the non-pregnant population.[1] In a large cross-sectional study of 53,477 non-pregnant adults, serum uric acid was positively correlated with fasting serum glucose and insulin resistance, as well as features of the metabolic syndrome, including waist circumference, low HDL cholesterol, hypertriglyceridemia, hypertension and fasting glucose ≥ 110 mg/dl.

A study by Di Cianni et al. in which serum uric acid was measured at a median of 16 months postpartum in women who had pregnancies complicated by gestational diabetes. Uric acid was significantly higher in women with metabolic syndrome (4.8 ± 1.2 mg/dl) versus women without metabolic syndrome (4.1 ± 0.8, $p<0.01$), independent of BMI, and metabolic syndrome is a known risk factor for developing type 2 diabetes.

We did not measure creatinine in order to adjust for glomerular filtration rate (GFR), but the majority of women would be expected to have normal excretion since we excluded women with prior diabetes, hypertension, kidney disease or major medical problems

Hyperuricemia has also been demonstrated to be a risk factor for developing type 2 diabetes. In our study, we found that uric acid $\geq$ 4.2 mg/dl early in pregnancy is associated with a 3-fold increased risk of developing gestational diabetes.

This study demonstrates a striking association between first trimester uric acid and risk of developing gestational diabetes, only half of the women with uric acid in the highest quartile actually developed the disease. This finding may be due to different pathways of development of gestational diabetes. Women who have a pregnancy complicated by gestational diabetes have up to a 50% chance of developing type 2 diabetes in their lifetime. It would be interesting to know whether these were the women with elevated uric acid in the first trimester.

The relationship of uric acid elevation in early pregnancy does indicate that metabolic state may affect adverse pregnancy outcomes. With the increase in both metabolic syndrome and obesity, more women are entering pregnancy with these conditions. It is possible that of the women who develop GDM, those with elevated first trimester uric acid are the women who are at risk to develop type 2 diabetes, and this warrants future investigation.

Thus we postulate that elevated first trimester serum uric acid helps in the prediction of gestational diabetes mellitus and also identification those at risk of developing type II Diabetes mellitus of follow up; also to counsel the patient about the short term and long term outcomes.

CONCLUSION

CONCLUSION

The objective of implementing an antenatal screening test for GDM is to identify pre-symptomatic women who will subsequently develop complications of pregnancy and implement efficacious treatment to reduce morbidity and mortality. Currently, complications of pregnancy due to GDM are not diagnosed until mid-late gestation.

It is important to recognize that by the time GDM is diagnosed in the late second or early third trimester of pregnancy, the 'pathology' is probably established and that reversal of the potential adverse perinatal outcomes may be limited. Many health professionals advocate the need for an earlier diagnostic/predictive test for GDM, one among them is "THE FIRST TRIMESTER SERUM URIC ACID".

A pregnant woman with high risk factors as marked obesity, strong family history of Type II DM, previous history of GDM, impaired glucose metabolism or glucosuria, History of neonatal death, History of fetal macrosomia, along with > 4.2 mg/dl is at risk of developing GDM.

The use of FIRST TRIMESTER SERUM URIC ACID as a predictor of GDM is simple, inexpensive, non invasive and easy to perform. This can be used as a screening test for the prediction of GDM.

Hence in routine antenatal care with predictive test like first trimester serum uric acid can be applied as a screening test for all women then this dreadful Gestational diabetes can be treated in time.

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PROFORMA

ELEVATED FIRST TRIMESTER SERUM URIC ACID AS A PREDICTOR FOR DIAGNOSING GESTATIONAL DIABETES MELLITUS

OUTCOME.

NAME : AGE: I.P. NO. :

SOCIAL STATUS : BOOKED/UNBOOKED:

LMP : G P L A

EDD : GESTATIONAL AGE :

DATE OF USG :

OBSTETRIC HISTORY :

MATERNAL ILLNESS :

GENERAL EXAMINATION :

HT. WT. PULSE: BP: TEMP:

ANAEMIA: EDEMA: CVS: RS:

OBETETRIC EXAMINATION

P/A :

USG

BLOOD INVESTIGATIONS-

- SERUM URIC ACID(<14 weeks)
- GCT (Glucose challenge test) - 24- 28 weeks.
- GTT (Glucose tolerance test).

MASTER CHART